with a nucleating factor(s) to promote actin motility. It is known that profilin and formins interact in such a manner. Thus, profilin-actin complexes may bind to the formin-homology (FH) domain of formin, which can in turn nucleate actin polymerization and bind to barbed ends processively as the filaments grow. Formin-profilin complexes can thereby cooperatively enhance filament elongation at barbed ends. However, Serio et al. (2010) tested six *Drosophila* formins, but none was required for *Rickettsia* motility, though it remains possible that these proteins play a redundant role. Alternatively, in a manner analogous to ActA in *Listeria*, the bacteria may itself encode a formin-like protein. In this regard, *R. rickettsii Sca2* is required for motility and virulence (Kleba et al., 2010); it will be interesting to see whether the protein encoded by this gene contains an FH-like domain that interacts with profilin.

Using *Rickettsia*, Serio et al. (2010) have revealed the function of a set of cytoskeletal proteins whose role in actin dynamics have been suspected but never so clearly defined. With *Rickettsia*, it will be interesting to see whether the RickA-Arp2/3 or Sca2-profilin complexes catalyze distinct actin-dependent processes during infection. Indeed, it may turn out that many pathogens use both actin polymerization systems. Such explorations may, in turn, elucidate novel regulatory signaling mechanisms as well as an understanding of how normal cells control actin dynamics.

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A Call to Arms: Interferons Prepare Bone Marrow Cells to Battle Peripheral Infections

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Viral infection leads to the rapid production of type I interferons within infected tissues. In this issue of *Cell Host & Microbe*, Hermesh et al. (2010) demonstrate that interferons produced following respiratory viral infection program leukocytes in the bone marrow to resist infection before trafficking to the lung.

Immune responses to viral infection of the respiratory tract are triggered by the innate recognition of pathogen-associated molecular patterns. One of the earliest antiviral responses is the synthesis of type I interferons (IFNs), which can signal back to the infected cell, as well as to surrounding cells, through the ubiquitously expressed IFNα/β receptor. Signaling through the IFNα/β receptor initiates a positive feedback loop, resulting in enhanced IFN production, the expression of genes that inhibit viral replication, and the amplification of the antiviral response (Moltedo et al., 2009). Concomitantly, a robust inflammatory response, including the production of cytokines and chemokines, serves to recruit leukocytes to the lung. Hermesh and colleagues now show that type I IFNs produced in the lung can interact directly with leukocytes residing in the bone marrow, activating antiviral transcription programs that protect these cells from infection with a wide range of viruses (Hermesh et al., 2010). Taken in broader context, these findings demonstrate that peripheral infections can "communicate" with leukocytes in the bone marrow, priming these cells to resist infection prior to their arrival in infected tissues, thus promoting their survival and assuring their ability to carry out antiviral functions (Figure 1).

The ability of type I IFNs to induce antiviral gene expression and inhibit viral replication within infected tissues has been well described (Katze et al., 2002). However, previous models for the effect of type I INFs on migrating leukocytes during peripheral infections assumed that IFNα/β receptor signaling, and expression of IFN-inducible genes, occurred once leukocytes migrated to infected tissues. Hermesh et al. (2010) used

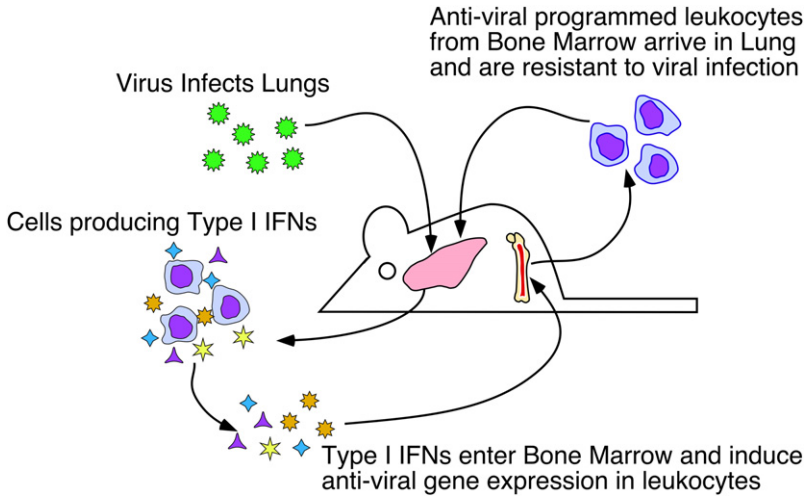

Figure 1. Type I IFNs Produced in the Lung following Respiratory Virus Infection Program Bone Marrow-Resident Leukocytes to Resist Viral Infection

Following respiratory virus infections, type I IFNs travel from the lung to the bone marrow, where they activate resident leukocytes. These leukocytes initiate an antiviral transcription program, rendering the cells resistant to viral infection prior to their migration from the bone marrow to the infected lung. Once in the lung, protected leukocytes promote viral clearance through the production of proinflammatory cytokines and chemokines.

murine models of influenza and parainfluenza virus infection to conclusively show that leukocytes in the bone marrow expressed IFN-inducible genes despite the fact that neither influenza nor parainfluenza viruses were detected in the blood or bone marrow. This is consistent with previous studies in both mice and humans, wherein type I IFNs were detected in the serum following influenza infection even though viral replication is limited to the lung (Hayden et al., 1998; Horisberger and De Staritzky, 1989). Therefore, the observed phenotype could only be due to the transport of cytokines from the lung, rather than from a low-level systemic infection. Importantly, using mixed bone marrow chimeras in which some leukocytes lacked expression of the IFNα/β receptor, Hermesh and colleagues show that type I IFNs, and not other inflammatory cytokines, are responsible for initiating the antiviral transcription program in bone marrow-resident leukocytes.

Although a role for bone marrow-derived leukocytes in immunity to respiratory viruses has been previously established (Lin et al., 2008), the importance of IFNα/β receptor signaling in these cells had not been investigated. Hermesh et al. (2010) find that type I IFNs produced following influenza and parainfluenza viruses induce the resistance of bone marrow leukocytes to infection by both RNA and DNA viruses, demonstrating that this mechanism can provide broad protection from many different pathogens. Most importantly, resistance to infection was essential for the antiviral functions of bone marrow-derived leukocytes once they migrated to the lung. They show that wild-type leukocytes recruited to the lung exhibit lower levels of viral RNA compared to IFNα/β receptor-deficient leukocytes. However, despite lower levels of viral RNA, wild-type leukocytes show significantly higher transcription of proinflammatory cytokines and chemokines. This enhanced resistance to infection and cytokine production had a significant impact on the course of infection, as chimeric mice in which the entire hematopoietic compartment had been replaced with cells lacking the IFNα/β receptor showed defective viral clearance.

Taken together, the data presented by Hermesh and colleagues show that leukocytes can be primed by type I IFNs in the bone marrow following respiratory virus infection, and these primed cells can infiltrate the lung to produce cytokines while being protected with viral infection. These findings demonstrate a previously unrecognized link between peripheral immune surveillance and the primary site of hematopoiesis, whereby type I IFNs serve as "messengers" that alert the sterile bone marrow to a localized infection. The communication between the periphery and the bone marrow during infection suggests several avenues for further investigation. First, although type I IFNs are detected in the blood during respiratory virus infection, it is not clear whether this is the sole route for delivering IFNs to the bone marrow. It is possible that travel through the lymphatic system, or low levels of localized production, may be important for the type I IFN-mediated instruction of bone marrow leukocytes. Second, the ability of localized peripheral infections to rapidly signal the bone marrow via type I IFNs may also influence recall responses because memory B and T cells are preferentially maintained in the bone marrow (Kohlmeier and Woodland, 2009). Finally, the data raise the possibility that immunosupressed individuals, who are often prone to viral infections, may benefit from low-dose type I IFN therapy. Overall, these findings show that appropriate instruction of bone marrow leukocytes is required for optimal control of respiratory viral infections and suggest a fundamental mechanism by which the localized infections can mobilize a systemic immune response.

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